Molecular, Cellular, and Systems Neuroscience

749-Pos Board B529
Mathematical Modeling of Melanopsin's Light Response in ipRGCs and Hek Cells
Phyllis R. Robinson[1], Abigail Jackson[1], Jessica Ortega[2], Hyewon Kang[2], Kathleen Hoffman[2].
[1]Biological Sciences, UMBC, Baltimore, MD, USA, [2]Mathematics and Statistics, UMBC, Baltimore, MD, USA.
Melanopsin is an unusual vertebrate photopigment that, in mammals, is expressed in a small subset of intrinsically photosensitive retinal ganglion cells (ipRGCs), whose signaling has been implicated in non-image forming vision, regulating such functions as circadian rhythms, pupillary light response, and sleep. The biochemical cascade underlying the light response in ipRGCs has not yet been fully elucidated, but is hypothesized to involve Gq pathway. We present both a deterministic and a stochastic model of the hypothesized melanopsin phototranduction cascade. Both models qualitatively reproduce experimental results under several different conditions. The models allow us to probe various mechanisms in the phototransduction cascade in a way that is currently experimentally not feasible.

750-Pos Board B530
A Mathematical Model of Melanopsin Phototransduction
Abigail C. Jackson, Jessica Ortega.
University of Maryland, Baltimore County, Baltimore, MD, USA.
Melanopsin is a recently discovered photopigment found in intrinsically photosensitive retinal ganglion cells (ipRGCs). It is involved in non-image forming vision, including circadian photoentrainment and the pupillary light reflex. It is also involved in light-related disorders, such as seasonal affective disorder. When light isomerizes the photopigment, a phototransduction cascade is activated, which produces an electrical signal that is sent to the brain. We developed a mathematical model of melanopsin's phototransduction pathway by using the law of mass action to convert chemical equations describing the pathway to a series of differential equations that was solved with MATLAB. Model parameters of the activation and deactivation were determined by fitting the model results to experimental calcium imaging data collected from transfected human embryonic kidney (HEK) cells expressing the melanopsin gene as well as electrophysiological data collected from ipRGCs. Mathematical simulations of a single flash response produce results consistent with those seen in the experimental data.
This work was funded by NSF for Undergraduate Biology and Mathematics Research Training, NSF IOSO721608 to P.R.R., NEI R01Y019053 to P.R.R.

751-Pos Board B531
Determining the Role of Melanopsin C-Tail in Deactivation and Trafficking
Elelbin A. Ortiz, Preethi Somasundaram, Evan Cameron, Phyllis Robinson.
University of Maryland, Baltimore County, Baltimore, MD, USA.
Melanopsin is a unique non-image forming visual pigment expressed in intrinsically photosensitive retinal ganglion cells in the vertebrate retina. These cells are involved in many non-image forming functions such as the photoentrainment of circadian rhythm and the pupillary light reflex. Melanopsin is deactivated through the phosphorylation of the C-tail followed by the binding of a β-arrestin molecule. β-arrestin contains a signal on its C-terminus that allows for internalization of G-protein coupled receptors (GPCRs) after inactivation. However, it is currently unknown whether melanopsin is internalized. Angiotensin II type 1A receptor (ATII1AR) and B2 adrenergic receptor (B2AR) are two GPCRs known to bind β-arrestin and undergo endocytosis. To study the role of the C-tail in melanopsin deactivation and trafficking, the C-tail of melanopsin is replaced with either ATII1AR or B2AR c-tail using cloning techniques. We then introduce our plasmids into Human Embryonic Kidney (HEK) cells to assess the localization and signaling of the constructs. Sequencing has confirmed that several chimeric constructs have successfully been made. Calcium imaging has confirmed that the Mel/B2AR chimeric constructs signals in a similar manner as melanopsin in the presence of light. These results will help determine the role of the melanopsin C-tail in its deactivation and trafficking.

752-Pos Board B532
Molecular Basis of Neuronal Signaling
Kin Lam[1], Zhe Wu[2], Klaus Schulten[1,2].
[1]Department of Physics, University of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]Center for the Physics of Living Cells and Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA.
A single-channel kinetic model was constructed for both sodium and potassium channels based on the kinetic rate of conformational rearrangement in the channels' voltage-sensor domains (VSD). The model reproduces observed conducting states of the channels and, more importantly, neural firing as described through the Hodgkin-Huxley (HH) equations. The modeling results indicate that neural signaling cast successfully in the form of HH equations can arise from a single sodium / potassium channel pair. The potassium channel gives rise to the (slow) n4 activation in the HH equations; the sodium channel VSDs I-III correspond to the (fast) activation variable m3 in the HH equations, while the sodium channel's VSD IV triggers inactivation with a similar rate as typically associated with the (slow) variable h in the HH equations. The sodium channel structure was constructed by homology modeling. Based on this structure, on sequence alignment and on mutation studies, key residues responsible for the kinetic difference between VSDs I-III and VSD IV can be identified. The results not only provide a linkage between molecular structure and neural firing behavior as seen in solutions of the HH equations, but also connect single ion channel conformational rearrangement with neuron signaling.

753-Pos Board B533
Inducible External Magnetic Fields Coupled to Injectable Synthetic Magnetic Nanoparticles Proposed to Replace Invasive Optogenetics as Modulators of Endogenous Ion Channel Gating
Edward J. Beck.
BioMagnetics, San Diego, CA, USA.
Optogenetics is poised to revolutionize the study of neural circuits and their roles in vivo. Two main components of this approach are indicated by that name. The first component is a light-gated ion channel gene (ICG) transfected into targeted neural circuits. The second, following gene transcription/translation, is an optical source focused on the transfected neural tissue. Light pulses gate transfected ion channel proteins leading to modulation of the host neuron's membrane potential (Na-selective ICG= depolarization and nerve cell excitation; K-selective ICG= hyperpolarization and nerve cell inhibition). Electrical signaling in untransfected neurons in synapse with transfected neurons is, in turn, modulated. The ultimate outcome of Optogenetics is a change in physiology or behavior supported by the targeted neural circuitry. Application of a magnetic field in close proximity to channel-attached magnetic nanoparticles is proposed as an innovation of Optogenetics. Such magnetic field gating of ion channels has advantages over Optogenetics. Most significantly, in contrast to invasive Optogenetics, magnetic field gating is speculated to gate ion channels by external, non-invasive magnetic fields. Commercially available magnetic nanoparticles make possible the essential magnetic field/ion channel connection. Magnetic field gating is proposed to innovate neuroscience research far beyond the limitations of Optogenetics. Furthermore, future translation of magnetic field gating technology to the health care market is far more practical than translation of invasive Optogenetics technology. Current applications using magnetic nanoparticles are described that lend credence to the hypothesis that magnetic fields can gate in vivo ion channels via attached magnetic nanoparticles. Magnetic field gating technology and technical challenges of developing this approach to gating ion channels are presented.

754-Pos Board B534
V220 Mutants of Ciona Voltage-Sensing Domain Based Genetically Encoded Fluorescent Voltage Sensors
Dhanarajan Rajakumar, Hong-hua Piao, Bok Eum Kang, Arong Jung, Eun Ha Kim, Bradley J. Baker.
Korea Institute of Science and Technology, Seoul, Korea, Republic of.
Genetically-encoded fluorescent voltage sensors enable the optical reporting of changes in membrane potentials. These sensors consist of a voltage-sensing domain of voltage-sensing phosphatase (usually from Ciona intestinalis Voltage-Sensing phosphatase) fused to a fluorescent protein (Super Ecliptic pHlorin A227D). To optically differentiate action potentials from subthreshold synaptic activity, residues in the voltage-sensing domain were mutated. Surprisingly one mutation, V220T in the S4 domain shifted the voltage response to more negative potentials, since this residue does not interact with the positively charged residues in S4 responsible for gating currents. To fine tune the voltage sensitivity of this probe, we mutated the V220 position extensively testing the remaining 19 amino acids. We found that tyrosine, phenylalanine, tryptophan, aspartate, threonine, and proline shift the voltage response substantially to more negative potentials enabling optical signals from hyper-polarizing voltages. Polar amino acids (glutamine, asparagine, alanine, and serine) vastly reduce the optical signal. Hydrophobic residues leucine, isoleucine, methionine, cysteine do not shift the voltage sensitivity to more negative potentials. We combined another mutant D164N (S2 domain) capable of shifting the voltage sensitivity to left with V220F and P. This combination further shifts the voltage response to more negative potentials and shallows the curve. These results suggest that the V220 residue interacts with the plasma membrane and could be mutated in conjunction with other